148

[Abstract Withdrawn]

149

ENGRAFTMENT AND IMMUNOLOGIC RECOVERY IN SIX ADULT PATIENTS TREATED WITH BUCYT AND HUMAN UMBILICAL CORD STEM CELL TRANSPLANTATION

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Between 6/2000 and 6/2003 six adult patients, age 26-58, received BuCyT followed by umbilical cord stem cell transplant for various diagnoses. AML = 2, ALL = 1, CLL = 1, myeloma = 1, and SAA = 1. All except one patient received 1 or 2 antigen mismatched stem cells. They received a median of 2.18 x 10 x 7 TNC/kg (range 1.48-3.12) and CD34 = 1.5 x 10 x 5/kg (range 0.4-4.2). Median time to ANC 500 was 26 days (range 15-46) and platelet 20,000 was 66 days (range 42-191). At 1 year, median CD4 count was 357 in 4 patients (range 264-715) and IgG level was 840 mg/dl (range 820-1640). All six patients had 100% donor engraftment documented by STR analysis as early as 1-2 months. Overall Grade III Acute GVHD was seen in 3 patients (2 skin and 1 gut). No Grade IV GVHD was seen. Limited chronic GVHD involving the skin and mucosa was seen in 4 patients. Two patients had recurrent CMV reactivation and in one of them it contributed to delayed platelet engraftment. One patient had bacterial meningitis caused by Flavobacterium Meningo Septicum and 1 patient had aspergillus sinusitis. With a median followup of 18 months (4-40 months), all 6 patients are alive and in remission/stable disease. In summary, umbilical cord stem cell transplant is an alternate source of stem cells for patients without matched sibling donors. Though the platelet engraftment may be delayed, the transplant related morbidity is small in this small group of poor risk patients.

IMMUNE RECONSTITUTION

150

SIGNIFICANT DECREASED LIPOPOLYSACCHARIDE (LPS)-ACTIVATED CYTOKINE/RECEPTOR, CHEMOKINE, IMMUNOREGULATORY, TRANSCRIPTION, APOPTOTIC, SIGNALING AND CELL STRUCTURE GENE EXPRESSION IN CORD BLOOD (CB) COMPARED TO ADULT PERIPHERAL BLOOD (APB) MONOCYTES BY OLIGONUCLEOTIDE GENE EXPRESSION MICROARRAY: INSIGHT INTO DIFFERENTIAL APB VERSUS CB MONOCYTE STRUCTURE AND FUNCTION

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Umbilical cord blood hematopoiesis and cellular immunity are developmentally immature when compared with adult peripheral blood (Cairo et al, Blood 90:4465,1997). We and others have demonstrated that umbilical cord blood transplantation (UCBT) is associated with decreased (grade III-IV) aGVHD, but delayed immune reconstitution (Abu-Ghosh/Cairo et al, BMT 24: 535,1999). Recently, the contribution of allograft monocytes to the induction of GVHD and/or immune tolerance has been demonstrated (Aranha et al, Haematologica, 87:219, 2002). Monocytes are critically important in the generation of cytokines, chemokines, immune mediators and the initiation of the cellular immune responses. We and others have previously demonstrated significant dysregulated cytokine gene expression and protein production and in vitro functional activities of activated CB versus APB MNC. In this study we compared, by oligonucleotide microarray, the differential gene expression profiles of basal and LPS-activated APB versus CB monocytes. Briefly, Mo were purified from fresh CB or APB (N = 5) and stimulated with LPS (10 μg/ml, 18 hours). mRNA was isolated, reverse transcripted to cDNA, labeled and hybridized to oligonucleotides (Affymetrix, U95A) (Huang et al, Science 294:870, 2001). Data was analyzed by Microarray Suite Version 5.0 (Affymetrix) and hierarchical clustering analysis was performed by GeneSpring 5.0 software (Silicon Genetics). Quantitative real time PCR (LightCycler-RNA amplification SYBR Green I kit, Roche Molecular Biochemicals) was used to examine selected genes to confirm expression levels. We demonstrated patterns of significant differential amplified gene expression in LPS-activated APB versus CB monocytes including cytokine (G-CSF, 14 fold), chemokine (MIP-1α, 5 fold), immunoregulatory (MHC DRB1, 5 fold), transcription factor (JunB, 4 fold), signal transduction (STAT4, 5 fold), apoptotic regulation (BAX, 5 fold) and cell structure (ladinin 1, 6 fold) among others. These results suggest that some of these differentially expressed genes may in part be responsible for the differences in the incidence and severity of aGVHD, immunoreconstitution and/or the ability to cross more disparate HLA barriers following UCBT. Moreover, these data provide insight into the molecular basis for differential cellular function and immune responses between activated CB and APB monocytes.

151

EXAMINING CYTOTOXIC EFFECTS ON THYMIC RECONSTITUTION: A MODEL

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A key component of long-term outcome after BMT is successful reconstitution of the immune system. Effective reconstitution of antigen-specific immunity requires de novo T cell generation. Bone marrow derived progenitors seed the thymus and undergo a complex process involving lineage commitment, proliferation and selection. This process requires coordinated interaction of marrow-derived lymphoid progenitors with thymic stromal cells. Disruption of the microenvironment can result in disrupted T cell lymphopoiesis. One cause of prolonged defects in generating functional T cells after BMT is damage to the thymic microenvironment. However, the impact of individual agents, administered at myeloablative or non-myeloablative doses, on the thymic microenvironment has not been fully evaluated. In addition, mechanisms by which stromal injury modifies T cell production and maturation have only begun to be understood. We have developed a model system using immunodeficient mice as a platform on which to assess thymic reconstitution. The thymus of mice deficient for the alpha chain of the IL-7 receptor (IL7R−/−) is relatively depleted of lymphoid cells and can be reconstituted following transplant of wild type marrow without prior myeloablative or immunosuppressive treatment. Injection of low doses of wild type bone marrow into these mice results in a normally cellular thymus repopulated with donor derived lymphocytes. The ability to achieve this reconstitution appears to depend on absolute numbers of early intrathymic precursors, rather than on total thymic cellularity. Our model system allows the evaluation of thymic reconstitution after single agent regimens insufficient to allow donor cell engraftment in wild type mice. We have exploited it to differentially assess the effects of cytotoxic agents including radiation and immunosuppressive drugs, on the capacity of the thymic microenvironment to support the maturation of normal lympoid progenitors. The effects of several agents on thymic reconstitution will be presented. For example, after low dose TBI (350rads), reconstitution is preserved, while after high dose (900rads)TBI it is not. It is anticipated that this information will lead to strategies to minimize delayed immune reconstitution and to augment T cell lymphopoiesis post-transplant. In addition, further evaluation of impaired thymic reconstitution will augment the understanding of lymphostromal interactions crucial to normal T cell lymphopoiesis.

152

IMMUNE RECONSTITUTION AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION INVOLVES PERIPHERAL T CELL APOPTOSIS

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